March 27, 2003

Sarah Loftus McLallen
Manager, CHEMSTAR
The American Chemistry Council Petroleum Additives Panel
Health, Environmental, and Regulatory Task Group (HERTG)
1300 Wilson Boulevard
Arlington, VA 22209

Dear Ms. McLallen:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for Dithiophosphate Alkyl Esters Category posted on the ChemRTK HPV Challenge Program Web site on November 27, 2002. I commend The American Chemistry Council Petroleum Additives Panel Health, Environmental, and Regulatory Task Group (HERTG) for their commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that The American Chemistry Council Petroleum Additives Panel Health, Environmental, and Regulatory Task Group (HERTG) advise the Agency, within 90 days of this posting on the Web site, of any modifications to its submission.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

-*S*-

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: C. Auer
A. Abramson
W. Penberthy
M. E. Weber

EPA Comments on Chemical RTK HPV Challenge Submission:
Dithiophosphate Alkyl Esters

Summary of EPA Comments

The sponsor, the Health, Environmental, and Regulatory Task Group of the American Chemistry Council's Petroleum Additives Panel, submitted a test plan and robust summaries to the EPA for Dithiophosphate Alkyl Esters dated November 11, 2002. The EPA posted the submission on the ChemRTK HPV Challenge Web site on November 27, 2002. The category consists of nine O,O-bis alkyl esters of phosphorodithioic acid.

EPA has reviewed this submission and has reached the following conclusions:

1. Closed-system Intermediate. The information provided in the test plan is not sufficient to support a closed-system intermediate claim.

2. Category Justification. The submitter's support for grouping the chemicals under this category on the basis of structural similarities is adequate. However, the submitter did not adequately support the proposed extrapolation of analog data to physicochemical properties, environmental fate and human health toxicity endpoints.

3. Physicochemical Properties and Environmental Fate. The submitter needs to provide measured boiling point, melting point, vapor pressure, partition coefficient, water solubility, stability in water, and biodegradation data for sufficient category members to allow for a read-across analysis to all other category members. The results of these tests will help interpret the results of ecological testing.

4. Health Effects. The submitter needs to provide adequate justification and supporting data for the assertion that these chemicals' corrosive properties preclude further testing. Absent adequate supporting data, the submitter needs to provide repeated-dose, reproductive, and developmental data on at least two category chemicals that encompass the molecular weight range of the category, as well as genetic toxicity testing on an additional substance.

5. Ecological Effects. EPA agrees that testing is necessary for the mixed 1,3-dimethylbutyl and isopropyl derivative but has reservations about the test plan. (a) EPA prefers that additional acute testing be conducted on mid- and end-range members. (b) The submitter needs to consider conducting a chronic daphnid test because there is a concern for both acute and chronic toxicity for this category. (c) EPA strongly encourages conducting testing at or below the water solubility limit, using mean measured concentrations.

6. Robust summaries. Robust summaries were not provided for most cited studies and data.

EPA is requesting that the submitter advise the Agency within 90 days of any modifications to its submission.

EPA Comments on the Dithiophosphate Alkyl Esters Challenge Submission

General

1. The submitter states that the category members are not transported to other sites or sold in acid form and are site-limited, closed-system intermediates. However, the level of information provided in the test

plan is not sufficient to support a closed-system intermediate claim under the Challenge Program (see guidance at http://www.epa.gov/chemrtk/closed9.htm).

2. Robust summaries are almost completely lacking. Summaries are necessary for calculated as well as measured values, and for all relevant studies on analogs.

3. Planned testing is insufficient to adequately characterize the category for all endpoint areas.

Category Definition

Generic structure: $(RO)_2P(=S)SH$ (R = C3 to C9, branched or linear)

84605-28-7	Phosphorodithioic acid, mixed O,O-bis(1,3-dimethylbutyl and isopropyl) esters
68784-30-5	Phosphorodithioic acid, mixed O,O-bis(sec-butyl and 1,3-dimethylbutyl) esters
113706-14-2	Phosphorodithioic acid, mixed O,O-bis(sec-butyl and isooctyl) mixed esters
6028-47-3	2-Pentanol, 4-methyl-, hydrogen phosphorodithioate
68649-43-4	Phosphorodithioic acid, O,O-dioctyl ester, branched
68516-01-8	Phosphorodithioic acid, mixed O,O-bis(isobutyl and pentyl) esters
68784-32-7	Phosphorodithioic acid, mixed O,O-bis(2-ethylhexyl and isobutyl) esters
5810-88-8	Phosphorodithioic acid, O,O-bis(2-ethylhexyl) ester
26999-29-1	Phosphorodithioic acid, O,O-diisoctyl ester

The category definition is adequately stated, although errors in the chemical structures in Table 2 of the test plan need correction. The structure for CAS No. 68516-01-8 appears as an *n*-propyl rather than an isobutyl group. The structure for CAS No. 68649-43-4 represents a specific octyl ester and should indicate the presence of other branched octyl groups, or other appropriate clarification. The structures for CAS Nos. 6028-47-3 and 5810-88-8 are transposed.

Category Justification

The justification for grouping these dithiophosphate alkyl esters into a category on the basis of their common functionality and limited structural variation appears appropriate for all endpoints. The estimated physical property values provided by the submitter, which need confirmation by selected measured data, suggest that the dithiophosphate esters will have low vapor pressures and water solubilities, and high octanol/water partition coefficients.

However, using data on the zinc mixed isobutyl, isooctyl and pentyl analog to support the category in lieu of testing for human health toxicity, physicochemical properties and environmental fate is not supported.

No health effects data for category members were provided in the robust summaries, although several studies were identified in the test plan. Data for the zinc salt of an analog were provided for acute dermal toxicity and acute inhalation toxicity tests. As noted in the health effects section below, neither of these studies is an adequate predictor of the toxicity of category members. Therefore, existing health effects data do not add support for the category.

Test Plan

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility).

The submitter estimated the physicochemical data using computer models such as EPIWIN for all category members. Measured values should be supplied for representative chemicals for boiling point, (decomposition points if appropriate), water solubility, vapor pressure, and octanol water partition coefficients following appropriate OECD guidelines. The use of estimated values introduces uncertainties that then become magnified in modeling applications. EPA suggests CAS Nos. 84605-28-7, 26999-29-1, and 68649-43-4 as representative test substances.

In addition, because the category members are acids, information on the pKa and solution pH of the substances is important to assessing data on other endpoints. An OECD guideline (#112) is available.

Partition coefficient. EPA guidance does suggest that estimation of Kow values is acceptable. However, estimation programs may not provide reliable estimated values for these acid esters. EPA recommends testing the octanol/water partition coefficients for the lower molecular weight substances (e.g., CAS Nos. 84605-28-7 and 68516-01-8); the pH may need to be controlled since the acid can dissociate.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity).

Photodegradation. The submitter needs to clarify the discrepancy between the statement in the test plan that the dithiophosphate alkyl esters do not contain chemical bonds that are UV absorbers and a comment that dithiophosphate alkyl esters' potential to "undergo direct photodegradation will be evaluated." The submitter's proposal to use estimated values to address indirect photodegradation appears appropriate.

Stability in water. Hydrolysis information was cited for CAS No. 5810-88-8 but without a robust summary showing experimental details such as pH. EPA disagrees that no further testing is necessary and suggests that stability in water testing according to OECD Guideline 111 be conducted initially on the lowest molecular weight chemical. If hydrolysis is >10 % after 5 days (half-life < 1 year), the substance is considered not hydrolytically stable and further testing may be needed on higher molecular weight species in this category.

Biodegradation. EPA disagrees with the submitter's conclusion that zinc salts of dithiophosphate alkyl esters necessarily behave similarly to the acid esters (no robust summaries were submitted for the proposed analogs). In addition, the analog CAS No. 54261-67-5, unlike the dithiophosphate alkyl ester category members, contains aromatic groups and has a much higher molecular weight. EPA recommends testing for CAS Nos. 84605-28-7, 2699-29-1, and 68649-43-4 to characterize members of low and high molecular weight and multiple branching, respectively.

Fugacity. The submitter proposes to estimate the fugacity of these chemicals using a Level I EQC model. Although EPA had previously recommended the use of EQC Level I, this model is somewhat limited. EPA now recommends a more rigorous Level III analysis. The EQC and EPIWIN Level III models are acceptable. Furthermore, the submitter needs to use measured physicochemical data as inputs so that the modeling will provide more accurate results.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity).

The submitter proposed no additional testing for acute, repeated-dose, reproductive, or developmental toxicity for any of the category chemicals on the basis that the category chemicals are used as site-limited intermediates, there is low risk of human exposure, and the category chemicals are extremely corrosive to tissues. EPA believes that none of these claims is adequately supported in the test plan.

EPA's conclusion is based on the following:

1. *Available health effects data on category members are not adequately described.* An oral LD50 value of 2.140 mL/kg was reported for the 2-ethylhexyl derivative in the test plan. Although a robust summary was not provided, the submitter reported no evidence that the test substance was irritating or corrosive via the oral route, nor was there any description of clinical signs or symptoms. In addition, an oral LD50 value of 2.140 mL/kg suggests that there may be a relatively high threshold for severe toxic effects when the 2-ethylhexyl derivative is administered orally. Therefore, it appears possible that oral toxicity tests can be conducted without excessive pain and suffering of the test animals.

The test plan also reports a dermal LD50 of 1.250 mL/kg for the 2-ethylhexyl derivative without an accompanying robust summary. There is no information on whether severe irritation or necrosis was observed. However, this information suggests that the test substance is more toxic via the dermal route versus the oral route of exposure.

2. The use of zinc salt derivatives as analogs may not be appropriate for health effects. The two robust summaries provided for health effects describe an acute dermal rat study and an acute inhalation rat study, respectively, both using the zinc salt of the mixed isobutyl, isooctyl, and pentyl derivative. The dermal study does show that the test substance caused severe irritation. However, the submitter did not indicate whether or how zinc contributes to the adverse effects.

3. More evidence is needed to justify the claim that the category members are corrosive to tissues via the oral route of exposure. Skin and eye irritation tests with the "C3-C8 dithiophosphate ester analog derivative" are described in the test plan. While irritation is not a SIDS endpoint, if, as the submitter claims, no health effects testing can be performed because of severe irritation/corrosion consequences, then more information on these studies would be useful. For example, were these performed with zinc salt derivatives? What are the pH values for the category members? The limited data cited for the 2-ethylhexyl derivative (see (1) above) suggest that the dermal route might be more irritating than the oral route. This may be due to pH changes on the skin versus the gut.

Overall, the claim that the category chemicals are too corrosive to test needs to be substantiated by reliable data, and it appears that toxicity tests that use a repeated-dose oral regimen may be conducted without excessive pain and suffering of the test animals.

Acute toxicity. EPA disagrees with the information in Table 6 (p. 24) that indicates that the acute inhalation toxicity data will be extrapolated to the category chemicals. These data are not adequate because the test substance was heated to 100°C to generate the test atmosphere, and the test animals were thus exposed to ~74 ppm H_2S and other unknown vapors. There also appears to be an error in the table on p. 27 of the submission. The table indicates adequate acute toxicity data for the 1,3-dimethylbutyl derivative, and a read-across approach for the 2-ethylhexyl ester. Since no data were supplied on the 1,3-dimethylbutyl derivative and LD50 values were cited for the 2-ethylhexyl ester, this appears to be a transposition error (this error also appeared in submitter's Table 2, as noted above under Category Definition). The table should indicate instead that acute toxicity data exist for the 2-ethylhexyl derivative, and that a read-across approach will be used for the 1,3-dimethylbutyl derivative. The data for the 2-ethylhexyl derivative, however, cannot be evaluated because robust summaries were not provided, and the dose units used in those studies need to be clarified (LD50 values of 2140 and 1250 mL/kg were reported for the oral and dermal studies, respectively, which appear to be unrealistic).

Repeated-Dose, Reproductive, and Developmental toxicity. No studies on the repeated-dose, reproductive, or developmental toxicity of any of the category chemicals or analog were available. The submitter reported that no testing on these endpoints is planned for reasons outlined above; however, in the absence of data substantiating the claim that these chemicals are closed-system intermediates and

supporting the conclusion that the chemicals are too corrosive to test, repeated-dose, reproductive, and developmental data (e.g., OECD 422) need to be obtained on at least two category chemicals that encompass the molecular weight range of the category using non-corrosive doses. Even if the submitter substantiates the claim that the category chemicals are closed-system intermediates, however, developmental toxicity data still need to be obtained because these data are needed for closed system intermediates. As indicated above, the submitter should consider using the oral exposure route because this is the preferred route for the HPV Challenge Program, and the available data suggest that the category chemicals may not be corrosive when administered orally.

Genetic Toxicity. No data are available on any of the sponsored chemicals or analogs. Therefore, the submitter plans to conduct an *in vitro* bacterial mutation assay and an *in vitro* chromosomal aberration assay on the lowest molecular weight member of the group (mixed 1,3-dimethylbutyl + iso-propyl derivative). The submitter also needs to conduct testing on a higher molecular weight category member in order to characterize the molecular weight extremes of the category.

Ecological Effects (fish, invertebrates, and algae).

No ecotoxicity data were provided. EPA agrees with the submitter's proposal to conduct acute fish, invertebrate, and algal toxicity testing on the mixed 1,3-dimethylbutyl and isopropyl derivative. However, EPA disagrees that no other testing is needed for this group of chemicals. EPA believes that the acute testing should also be conducted on a mid-range member (CAS No. 6028-47-3) and a category anchor chemical such as CAS No. 26999-29-1 to clarify the influence of log Kow, surfactant properties, and water solubility on the toxicity to aquatic organisms.

Because of the predicted log Kow values of $\geq$4.48 and the potential for surfactant activity with longer alkyl chains, EPA recommends chronic invertebrate toxicity testing for any of the dioctyl esters. All three are expected to show similar chronic toxicity in invertebrates as all have the same calculated log Kow value.

EPA strongly encourages conducting testing at or below the water solubility limit, using mean measured concentrations.

Specific Comments on the Robust Summaries

The submitter provided robust summaries only for two mammalian acute studies.

Followup Activity

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.